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Trichloromethyl-heptyl Carbinol

by

Frank Borg

Presented in partial fulfillment of the
requirement for the degree of
Master of Arts.

State University of Montana

1934

Approved:

J. W. Howard
Chairman of Examining Committee

W. S. Bateman
Chairman of Graduate Committee

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Trichloromethyl-heptyl Carbinol

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Historical

The alcohols containing the trichloromethyl group have been an object of study since at least 1881, when Willgerodt recorded his studies on chlorotone in the German journal, Berichte der deutschen Chemischen Gesellschaft. From that time on considerable interest has been shown in these trichloromethyl alcohols. The work done on these compounds has been in their various methods of preparation and their use. The greatest value of these alcohols lies in their application as a medicine.

In the preparation of these trichloromethyl carbinols a number of methods have been employed. The procedures most extensively used are the condensation of chloroform with a ketone or aldehyde in the presence of potassium hydroxide, and the condensation of chloral with an alkyl magnesium halide; while the reduction reaction of chloral in a secondary alcohol with aluminum ethylate, aluminum alcoholate, or an aluminum halogen alcoholate, and the fermentation of sugar in the presence of chloral have each given satisfactory results.

Compounds containing the trichloromethyl and carbinol groups have been prepared in both the aliphatic and aromatic series as is shown by the fact that results have been recorded in the straight chain hydrocarbons from C_2 to C_9 , with the exception of C_8 and C_7 . The latter has been prepared but not published. While in the ring compounds trichloro-

methyl-benzyl carbinol,^{#16} trichloromethyl-furan carbinol,¹⁵ and trichloromethyl-phenyl carbinol¹⁵ have been prepared and studied by J. W. Howard. Trichloromethyl-cyclohexyl carbinol has been prepared but not recorded.

The medicinal value of these compounds lies in their antiseptic, antispasmodic, hypnotic, and anesthetic properties, as has been shown in many experiments.

Beginning with trichloroethanol, which is the simplest trichloro alcohol recorded in the literature, one finds that it has been prepared from the fermentation of sugar by beer yeast in the presence of sodium dibasic phosphate and chloral, giving a seventy percent yield of the desired alcohol.³¹ This compound has also been prepared by allowing a solution of chloral in a secondary alcohol to react with an aluminum alcoholate or an aluminum halogen alcoholate.⁸ R. Dworzak⁵ obtained this alcohol in poor yields by treating chloral with aluminum ethylate. In medicinal work on this trichloroethyl alcohol it was found to be one-half decomposed in a urine analysis taken on rabbits to which it had been administered.¹

In the preparation of the $C_3H_5Cl_3O$ compounds, reference has been made only to the trichloro-isopropyl alcohol member of this group, which is commonly known under the trade name

#Note: all references will be found in numerical order in the Bibliography on page 32 of this paper.

of isopral. Isopral has been prepared only by the condensation of chloral with methyl magnesium halide under the general procedure of the Grignard reaction, as is shown by Howard¹⁸ and Henry¹³ in their work. This reaction, which is the basis for many organic reactions, is the typical method by which most of the compounds are made in this trichloromethyl carbinol series. Isopral cannot be made by the condensation of chloroform and acetaldehyde in the presence of potassium hydroxide, as was proven by J. W. Howard.¹⁵ This above reaction is the other general method of preparing members of this trichloromethyl carbinol series.

Isopral is used in medicine as a hypnotic.⁴ Impens¹⁹ found that a ten percent solution of this alcohol will prevent the fermentation action of the yeast cell. This compound is prepared on a commercial scale, and has furnished the basis for the first of a series of studies as to the effect on the physiological action by replacing the methyl group by the trichloromethyl one. Howard and Stimpert¹⁸ found as a result of their studies of the guinea pigs that isopral is more toxic than isopropyl alcohol. Macht²³ proved that isopropyl alcohol was less toxic than propyl alcohol but two times as toxic as ethyl alcohol. His studies were made on the cat. As a comparison of the disinfectant powers of isopral and isopropyl alcohol, Howard and Stimpert¹⁸ found that isopral has about twelve

times the disinfectant power of the isopropyl alcohol. This compound is also recommended as an anesthetic when mixed with hedonal for it facilitates the completion of anesthesia by gas and reduces the duration of it by a preliminary use of these compounds.²¹ The speed by which narcosis may be induced may be expressed as, paraldehyde is greater than isopral in an ether solution, is greater than urethane, is greater than ethyl alcohol. Tests show that there is no comparison between these speeds of reaction and their biological action.²²

Of all the compounds of this trichloromethyl carbinol series, chlorotone was the first prepared and studied. Willgerodt³⁰ prepared this member in 1881 by the condensation of twenty-five grams of chloroform and twenty-five grams of acetone in the presence of five grams of potassium hydroxide. He also tried sodium hydroxide which was found to work very slowly, and calcium hydroxide which failed to give the desired results in the place of the potassium hydroxide. Guédras¹¹ has also studied chlorotone, and his results conform to those of Willgerodt. This trichloro-tertiary-butyl alcohol has also been prepared by the Grignard reaction. M. Taffe²⁸ made chlorotone by the methods of Willgerodt and Grignard, as well as its acetic and benzoic esters. In this $C_4H_7Cl_3O$ group, the trichloromethyl-ethyl carbinol member has been prepared by J. W. Howard¹⁶ using the Grignard method with

ethyl bromide. Reference is made to 1,1,1. trichloro, 2, methyl propanol in the literature, but no method of preparation was given. It is used, however, as a plasticizing agent when mixed with cellulose acetate.²

Of all the trichloromethyl carbinols, chlorotone has the largest and most varied use. Its most outstanding application is in the field of medicine where it is used as an antiseptic,¹⁷ antispasmodic,¹⁷ brain stem hypnotic,¹⁴ and as a local anesthetic.¹⁷ Chlorotone and thyroxine injected into rabbits caused an increased diuresis in deep chlorotone, while a light chlorotone inhibited it.⁷ These above results were found after a peroral intake of water. In another case, the diuretic action of paraldehyde²⁹ upon rabbits is increased by the denervation of the kidneys, and the inhibitory action of chlorotone and pituitrin upon diuresis is not affected, and the ability of the kidneys to concentrate salts is only slightly decreased. Chlorotone will also inhibit diuresis caused by caffeine, sodium sulfate, and urea.²⁴ In work with dogs, chlorotone inhibits diuresis very markedly even in subhypnotic doses for fifteen to thirty minutes, and suffices to inhibit diuresis for twenty-four hours to forty-eight hours.³ Under its anesthetic properties, a glycol solution of chlorotone has been used as an anesthetic for cats and dogs.¹² A one-half cubic centimeter of the forty percent solution in glycol

per kilogram body weight, injected intraperitoneally, is sufficient to maintain an animal in a satisfactory state of anesthesia. This mixture seems to possess all of the advantages and none of the disadvantages of the older ten percent chlorotone olive oil solutions. Another advantage claimed for chlorotone as an anesthetic²⁷ is the production of a rapid and complete anesthesia lasting from twelve to forty-eight hours with a single injection of four tenths grams per kilogram body weight. It is easily administered, requires no attention, and gives a steady plane of anesthesia. The drug acts for a long time and death occurs in the above dose in one to three days. Recovery of the animal is possible with one-half of this dose, supplementing with morphine as anesthesia is desired. Chlorotone, when used as a preservative of organic substances, is injurious to the circulation by its paralyzing effect on the heart muscles and the motor cardiac centers.²⁶ A chlorotone²⁵ solution is also used to wash organisms from agar slants in the making of bacterial suspensions. There is no clumping of the organisms as with the tricresol preparations, and the anesthetic properties of chlorotone make the use of such a vaccine most acceptable to the patient. The chlorotone also preserves sterility.²⁵

Of all the $C_5H_9Cl_3O$ compounds possible, the tri-chloro-tertiary-amyl alcohol, the trichloromethyl-pro-

pyl carbinol, and the trichloromethyl-isopropyl carbinol members have been made. The trichloro-tertiary-amyl alcohol was prepared by Ekeley and Klemme⁶ by the addition of one molecular part of methylethyl ketone to two molecular parts of chloroform in the presence of powdered potassium hydroxide. The product was fractionated by distillation, dried over anhydrous sodium sulfate, and then distilled in vacuo. Twenty-five grams of methylethyl ketone gave eight to ten grams of the alcohol. The other two members, namely trichloromethyl-propyl carbinol¹⁶ and trichloromethyl-isopropyl carbinol,¹⁷ were prepared by J. W. Howard by means of the Grignard reaction. Propyl bromide and isopropyl bromide, respectively, were treated with magnesium turnings and chloral to give the desired products. The dichloro-derivative of the trichloro-tertiary-amyl alcohol possesses real therapeutic value. It was used in the World War by the British⁶ as an anodyne and as a mild antiseptic when mixed with dessicated antitetanic serum.

In the $C_6H_{11}Cl_3O$ series trichloromethyl-butyl carbinol has been prepared by J. W. Howard.¹⁷ It was made from butyl bromide using the Grignard reaction.

Trichloromethyl-amyl carbinol has been made in the $C_7H_{13}Cl_3O$ series by J. W. Howard. It has not been recorded in the literature as yet.

Formaldehyde, acetaldehyde, propionic, butyric, and isovaleric aldehydes have been used with chloroform in the

presence of potassium hydroxide by J. W. Howard, but all gave negative results as to the formation of the desired trichloromethyl carbinols.¹⁵ Ekeley and Klemme attempted to condensate chloroform with diethyl, dipropyl, ethylpropyl, and methyl-isobutyl ketones, but all gave unsatisfactory results.⁶

Very few compounds containing the trichloromethyl and carbinol groups have been prepared in the ring or aromatic series. Trichloromethyl-furan carbinol has been prepared by J. W. Howard.¹⁵ This alcohol was made by the condensation of furfural and chloroform in the presence of potassium hydroxide. A condensation product was formed by this same general reaction with potassium hydroxide, benzaldehyde, and chloroform, giving trichloromethyl-phenyl carbinol.¹⁵ Jocić²⁰ studied this reaction, and Yoder³² states that he prepared this compound. As no experimental data was given, J. W. Howard¹⁵ repeated this work to find the best experimental methods and the physical constants for this alcohol. Trichloromethyl-cyclohexyl carbinol has been prepared by R. Browne, but as yet has not been recorded. The last known compound, trichloromethyl-benzyl carbinol, was prepared by the Grignard reaction using benzyl chloride by J. W. Howard.¹⁶ Its acetic and benzoic esters were also made.

Two other members of the aromatic trichloromethyl carbinols have been attempted, namely, the condensation of salicylaldehyde and chloroform by Howard¹⁵ and the conden-

sation of acetophenone and chloroform by Ekeley and Klemme.⁶ However, these attempts gave unsatisfactory results.

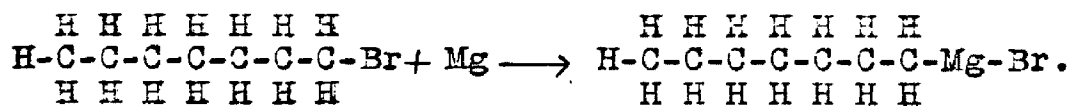
Theoretical

Carbinol Preparation

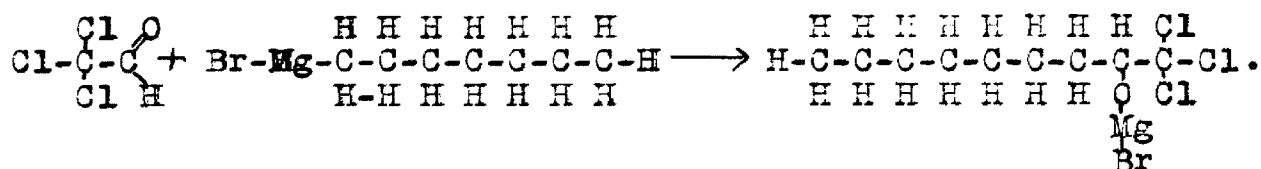
The method used in the preparation of trichloromethylheptyl carbinol was that of Grignard who discovered the process around 1900. His discovery of organo-magnesium compounds and their reaction has been of great value in the synthesis of many organic compounds. A rising interest is being shown in this general type of reaction as the amount of recorded material is being greatly increased every year. This particular reaction has been shown to work in the preparation of other analogous compounds in this series. The purpose of this study is to add another member to the known series and to give its properties.

In the preparation of the Grignard reagent a three necked liter flask was used. Into the middle neck a mercury sealed automatic stirrer was fitted and into the other necks a dropping funnel and a reflux condenser were fitted. All apparatus was thoroughly dried, and a calcium chloride tube was placed at the top of the reflux condenser to keep out any water vapor from the air. Into the flask was placed the magnesium and an iodine crystal. A mixture of absolute ether and heptyl bromide was introduced through the dropping funnel, and, when it was

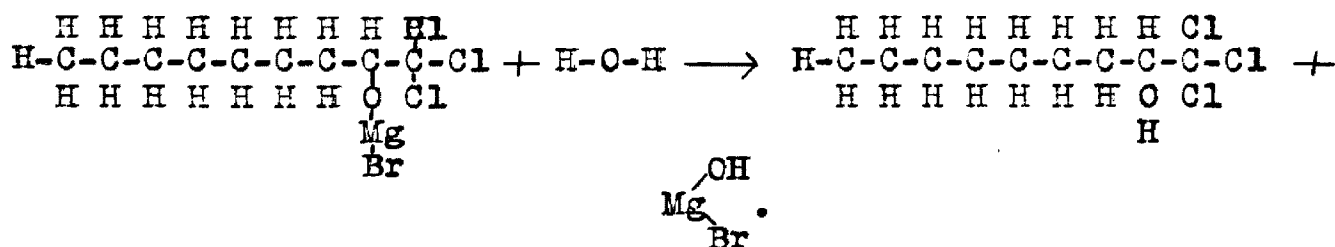
allowed to come in contact with the magnesium, a vigorous reaction took place. The speed of this reaction could be regulated by the amount of ether and heptyl bromide added to the magnesium. The product formed is called a Grignard reagent and is formed as follows:



In order to add the trichloromethyl group this above Grignard reagent was treated with a mixture of chloral and absolute ether. The ether was used to dilute the chloral. Here again a vigorous reaction took place and the speed of this reaction was regulated by the rate of addition of the chloral. The reaction between the chloral and the Grignard reagent may be shown as:



The compound resulting from the above process is hydrolyzed with water and a thirty percent solution of sulfuric acid. The speed of this reaction could also be regulated by the rate of addition of acid and water. This last reaction gives the desired product, trichloromethyl-heptyl carbinol.



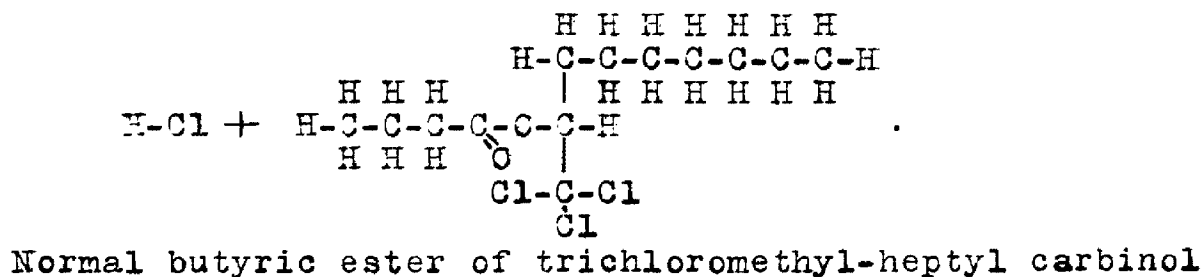
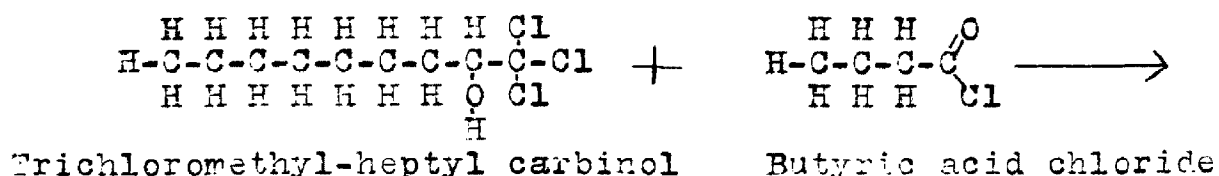
At the end of the above process there were two separate layers in the liter flask, a top dark brown ether layer, and a water and acid layer below. These two layers were separated by means of a separatory funnel, the ether layer being saved. This mixture was washed with distilled water, a solution of sodium carbonate, sodium bisulfite, and then rewashed with water. The ether solution was allowed to dry over anhydrous sodium sulfate. The ether was distilled from the carbinol mixture, and the resulting product was distilled under a reduced pressure of between seven and fifteen millimeters. All fractions were saved from the temperature of the lowest boiling one up to the temperature at which the remaining liquid in the flask began to decompose. In all trials a tarry residue was left in the flask.

From the above fractional distillation under reduced pressure, a number of samples were obtained. In order to find the fraction containing the compound sought, the chlorine content of each sample collected was analyzed by the Carius method. Trichloromethyl-heptyl carbinol contains 42.97 percent chlorine by weight. Samples were collected that had a chlorine content which was in close conformity to this figure. In order to be sure that these fractions contained the trichloromethyl-heptyl carbinol sought, an ester was prepared and its chlorine content was determined by the Carius method also. The

normal butyric ester of trichloromethyl-heptyl carbinol has a chlorine content of 33.50 percent by weight. Results in the ester analysis proved that the ester sought was prepared, and that trichloromethyl-heptyl carbinol was the basis for this latter compound.

Ester Preparation

In the preparation of the normal butyric ester of trichloromethyl-heptyl carbinol, the alcohol was refluxed with butyric acid chloride. This reaction may be shown as,



Carius Method

The Carius method used in the determination of halogens consists of heating the compound containing the halogen with concentrated nitric acid and silver nitrate under pressure in sealed glass tubes. The amount of silver halide formed is estimated by gravometric means using a Gooch crucible. This determination is carried out in sealed tubes made of thick-walled special glass. One end of

the tube is sealed in such a manner as to give a round blunt end. The tube, or bomb, is then thoroughly washed and dried. Into the bomb is placed about one and one-half grams of silver nitrate crystals, and from one and one-half to two cubic-centimeters of concentrated, halogen-free nitric acid. This acid is introduced by means of a long pipette so that no drops of acid are allowed to come in contact with the upper part of the tube. Any acid in the top part of the tube will cause it to crack in the subsequent sealing. The compound to be analyzed for its halogen content is now weighed into a small sodium decomposition tube. This tube is then introduced into the bomb in such a manner that it slides slowly down the inner surface until it reaches the bottom. The open end of the bomb is now sealed off in the form of a thick-walled capillary. During this sealing it is imperative that the contents of the bomb are not mixed, as a gas will be formed which will hinder the sealing operation. In order to check the halogen content of each fraction, three determinations on each were run. These tubes are then wrapped in heavy paper to insure even heating and placed in a bomb furnace. They are heated from 225° to 250° C. for four hours. After the furnace has cooled, the tubes are opened while still in the oven. The capillary ends of the tubes are heated and the internal pressure, formed by the reaction, blows a small hole in the tip. The bombs can then be safely removed from the

furnace, and a hole made in them large enough to allow the precipitate of silver halide and the sodium decomposition tube to be removed. The contents of the Carius tube are washed into a beaker by means of distilled water. The tubes are washed until all the silver halide has been removed. The sodium decomposition tube is removed from the beaker and washed free of any clinging precipitate. The contents of the beaker are boiled and the lumps of silver halide are broken up to insure that all the silver nitrate will go into solution. The contents of the beaker are allowed to cool, and then washed into a Gooch crucible with distilled water. The precipitate left in the crucible is washed until the filtrate shows that no silver nitrate remains when tested with hydrochloric acid. The Gooch crucibles are put into an oven for an hour to dry, allowed to cool in a dessicator, and then weighed. The percentage of halide in the sample used may be calculated from its weight and the weight of the silver halide found.

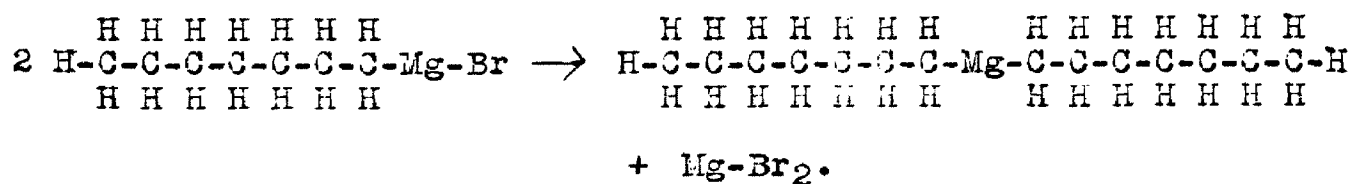
Yields

The yields in all cases were very poor due to experimental methods and due to the probability of a number of side reactions. A great deal of work has been done on the Grignard reagent as to the factors which affect the yield. H. Gilman,¹⁰ who has done extensive

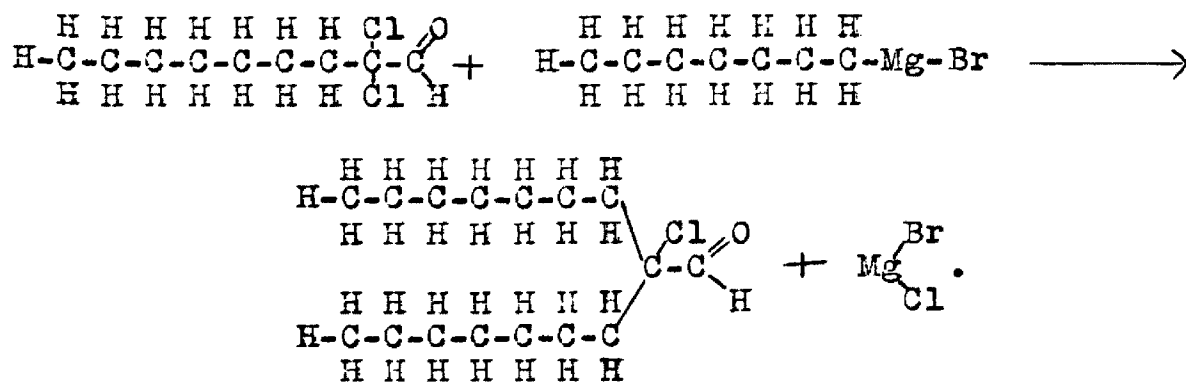
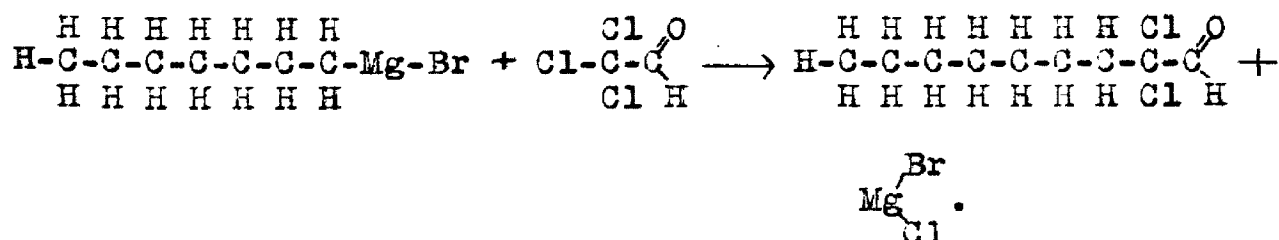
work in this field, reports that increased yields are found with proper temperature control, extensive stirring, and the use of small amounts of ether as a dilutant; also, the faster the addition of the alkyl halide, the lower the yield, and the finer the magnesium, the greater the yield. He also states that the odd-numbered carbon chains give lower yields than the even-numbered carbon ones just above them in the same series. Gilman⁹ has also proved that the following reaction takes place in the Grignard solution:

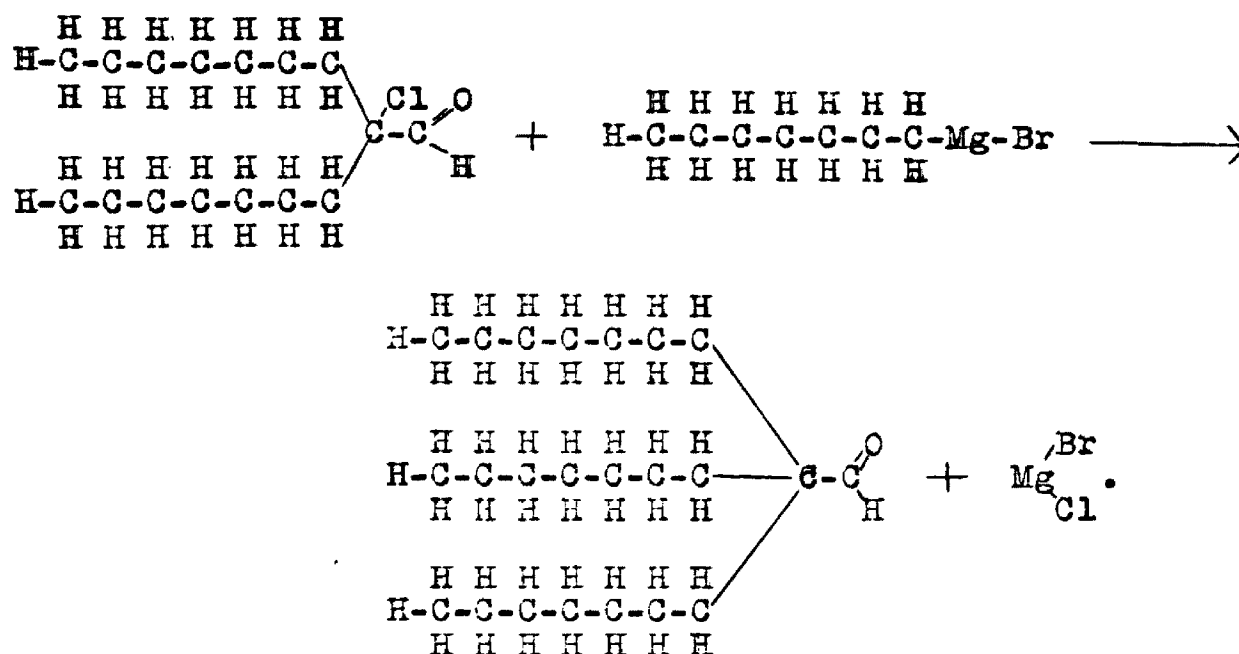


or, as in the case at hand,

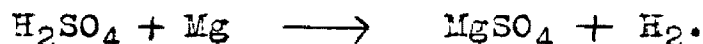


There are a great number of other possible side reactions as,

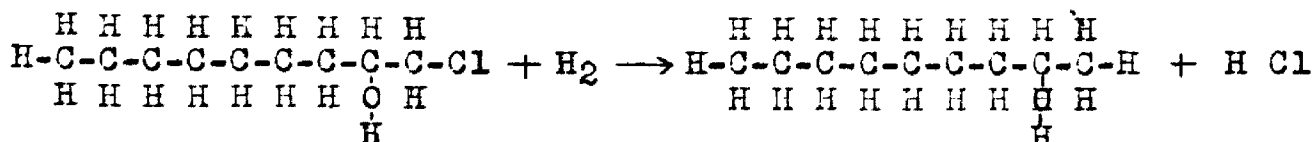
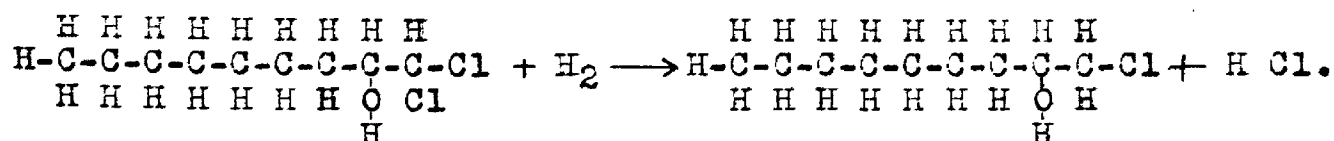
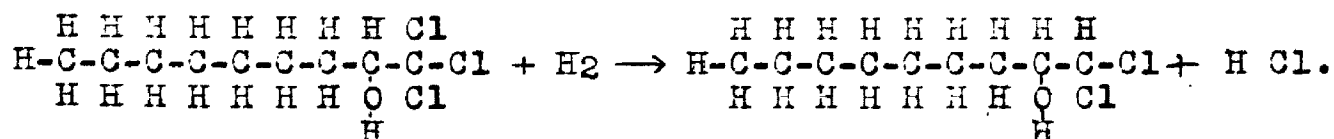




If there is any unchanged magnesium left in the Grignard solution, the magnesium when treated with the thirty percent sulfuric acid will liberate hydrogen as,



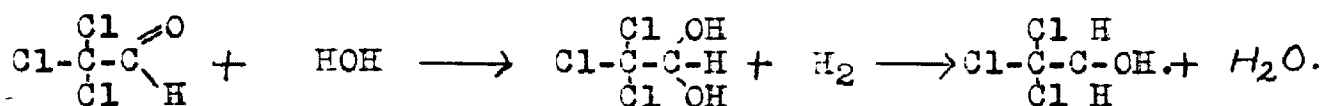
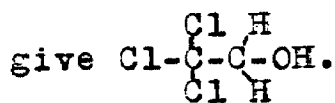
This free hydrogen may react with the trichloromethyl-heptyl carbinol as follows:



It was found from experiment that when the Grignard solution was decanted from the unchanged magnesium, greater yields

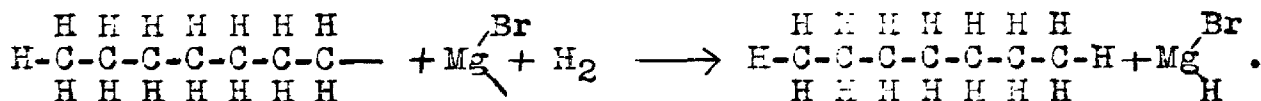
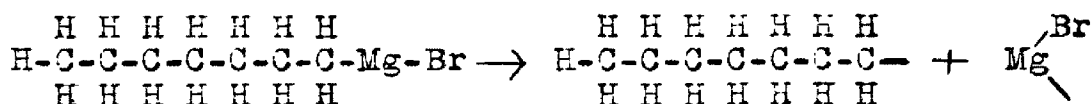
were obtained.

If the apparatus had not been absolutely dry, the water might have reacted with the chloral to give chloral hydrate, which in turn might react with the free hydrogen generated to

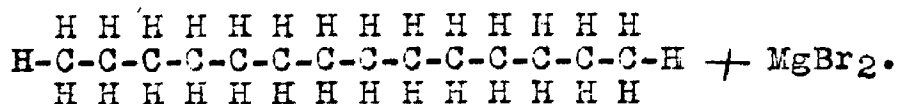
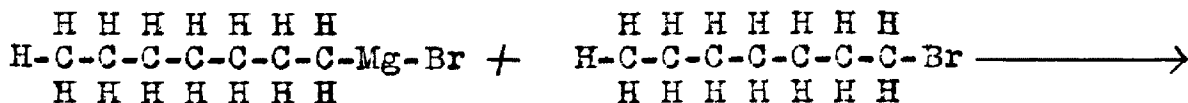


Gilman⁹ suggests $\text{R-Mg-X} \rightarrow \text{R-} + \text{-Mg-X}$ as a reaction.

These two products may react with free hydrogen to give a result as,



The Grignard solution of heptyl-magnesium-bromide can react with another molecule of heptyl bromide to give



Experimental

Materials.

For the success of the experiment it is necessary to have all materials and apparatus thoroughly dry.

The alkyl radical in the trichloromethyl-heptyl carbinol was obtained from heptyl bromide. This heptyl bromide was acquired from the University of Illinois through the courtesy of Dr. Fuson.

The magnesium used in the first four proctals was in the form of turnings which had been cleaned with alcohol and then washed twice with ether. The turnings were dried in an oven and kept in a dessicator until used.

Absolute ether was prepared by allowing commercial ether to remain over granular calcium chloride over night. The ether was separated from the calcium chloride and distilled over phosphorus penta-oxide. This distillate was collected in a flask containing freshly cut metallic sodium which would remove any possible remaining water.

Chloral was always freshly prepared before being used. This chloral was prepared by distilling chloral hydrate over concentrated sulfuric acid.

The iodine, sodium carbonate, sodium bisulfite, anhydrous sodium sulfate, and sulfuric acid used, were of high chemical purity.

Protocols.

Protocol 1. In the preparation of the Grignard reagent, six grams of magnesium turnings and an iodine crystal were placed in the liter flask. To this a mixture of forty-five grams of heptyl bromide in forty cubic centimeters of absolute ether was slowly added through the dropping funnel.

About forty-five minutes were required for the addition of the alkyl halide and ether mixture. The resulting Grignard reagent was stirred occasionally during an hour of refluxing, and then allowed to stand over night. At the end of this process there was some unchanged magnesium and a white precipitate at the bottom of the flask, and a muddy appearing layer on the top. The next day thirty-seven grams of chloral in seventy-five cubic centimeters of absolute ether were added through the dropping funnel over a period of one hour. The speed of this reaction was regulated by the rate of addition of the chloral ether mixture. The solution in the flask was refluxed for another hour with occasional stirring, and allowed to stand over night. A hard crust was formed in the flask on standing. To the mixture in the flask distilled water was slowly added until no further action was noted. The crust was changed into a heavy, dark brown, jelly-like precipitate by the action of the water. The speed of this reaction could also be regulated by the rate of addition. The solids left in the mixture were dissolved with a thirty percent solution of sulfuric acid. The acid was slowly added until no further reaction took place. At this time there were two separate layers in the flask, a lower water and acid one, and a top layer of ether containing the carbinol, which was saved. These two layers were separated by means of a separatory funnel. This ether layer was washed in turn with distilled water, a saturated

solution of sodium carbonate, a saturated solution of sodium bisulfite, and then rewashed with water. The carbinol mixture was dried for twelve hours over anhydrous sodium sulfate. The purpose of the sodium carbonate is to neutralize any sulfuric acid that may be left in the mixture. The sodium bisulfite was used to remove any remaining chloral. The last water washing was to remove any of the two salts which might have remained. This purified ether mixture was transferred to a Claisen distilling flask and the ether was removed by distillation. The remaining liquid in the Claisen flask was fractionally distilled under reduced pressure. During this process glass tubes and beads were placed in the distilling flask as a precaution against frothing. At the end of the distillation a tarry residue remained in the flask. This was discarded. The mixture in the Claisen flask was divided into the following fractions:

Number	Temperature	Greatest Yield	Pressure
1.	51-70° C.		8 mm.
2.	70-80° C.	74-75° C.	8 mm.
3.	80-109° C.	106° C.	10.5 mm.
4.	109-120° C.	118° C.	9 mm.
5.	120-140° C.	127° C.	9 mm.

Above 140° C. the tarry residue began to decompose.

The chlorine content of fraction number four was

analyzed by the Carius method. Number four was chosen because it contained the largest amount of distillate.

This sample gave in percentage of chlorine:

Number	Percentage Found	Percentage Calculated
1.	39.25	42.97
2.	41.26	
3.	41.15	

The results from protocol one were promising, so the quantities of the reacting substances were increased, as insufficient material was obtained to form a working body.

Protocol 2. In this run fifteen grams of magnesium turnings were treated with ninety grams of heptyl bromide in eighty cubic centimeters of absolute ether. The heptyl bromide and ether were slowly added to the magnesium over a period of one hour. This mixture was refluxed for four hours and allowed to stand over night. A white precipitate was formed as before. The following day seventy-four grams of chloral in one hundred and fifty cubic centimeters of absolute ether were slowly added. The speed of this reaction was regulated as in protocol one. This mixture was refluxed for three hours and allowed to stand over night. As before a heavy, jelly-like precipitate was formed by the action of the distilled water. This water was added until no further action was noted, and the mixture was then treated with the thirty percent solution of sulfuric acid. The mixture was

separated and the ether layer was washed, treated with sodium carbonate, sodium bisulfite, rewashed with water, and then allowed to dry over anhydrous sodium sulfate. It was fractionated, and the residue was discarded. The chlorine content of the fraction between 112° and 123° C. was analyzed. The carbinol solution was divided into the following fractions:

Number	Temperature	Greatest Yield	Pressure
1.	$55-70^{\circ}$ C.	57° C.	13 mm.
2.	$70-80^{\circ}$ C.		13 mm.
3.	$80-100^{\circ}$ C.	$89-92^{\circ}$ C.	13 mm.
4.	$100-112^{\circ}$ C.	107° C.	15 mm.
5.	$112-123^{\circ}$ C.	$121-122^{\circ}$ C.	15 mm.
6.	$123-132^{\circ}$ C.		15 mm.

Above 138° C. the tarry residue began to decompose.

Carius determinations were run on fraction number five and gave the following percentages of chlorine:

Trial	Percentage Found	Percentage Calculated
1.	44.90	42.97
2.	43.33	
3.	44.97	
4.	44.86	

There was a yield of five grams in fraction five.

At this time the fractions of protocols one and two

were combined and refractionated into the following:

Number	Temperature	Greatest Yield	Pressure
1.	70-85° C.		9 mm.
2.	85-105° C.		9 mm.
3.	105-110° C.	108° C.	9 mm.
4.	110-117° C.	115° C.	9 mm.
5.	117-124° C.	121° C.	9 mm.
6.	124-135° C.	121	9 mm.

Above 135° C. the residue began to decompose.

The chlorine content of fraction number five was determined.

Trial	Percentage Found	Percentage Calculated
1.	34.37	
2.	33.50	42.97
3.	33.62	

The chlorine content of fraction number four was determined. It gave:

Trial	Percentage Found	Percentage Calculated
1.	41.92	
2.	42.96	42.97
3.	42.04	

At this time the work was interrupted for three

weeks and the chlorine content of fraction number four was rechecked.

Trial	Percentage Found	Percentage Calculated
1.	40.61	42.97
2.	39.41	
3.	39.82	

From the above results the conclusion may be drawn that the compound decomposes on standing. The freshly distilled fraction gave an average chlorine content of 42.30 percent, while the fraction on standing showed an average chlorine content of only 39.94 percent.

Protocol 3. At this time another carbinol mixture was made, but unsatisfactory results were obtained as to the finding of the desired product. The procedure in this trial was the same as that carried out in **protocol two**.

Protocol 4. In view of the fact that unsatisfactory results were found in **protocol three**, a slightly different procedure was followed here. Fifteen grams of magnesium turnings with a crystal of iodine were placed in a liter flask. This was treated with ninety grams of heptyl bromide in eighty cubic centimeters of absolute ether. The ether and heptyl bromide were slowly added to the magnesium over a period of one hour. This mixture was refluxed for four hours and allowed to

stand over night. A white precipitate was formed as before. The following day this mixture was added to seventy-four grams of chloral in one hundred and fifty cubic centimeters of absolute ether. This was done in hopes that a more complete reaction could be obtained. As the Grignard reagent was added, the reaction which took place could be followed until all the reagent had been added. This mixture was refluxed for three hours and allowed to stand over night. When the distilled water was added, the hard crust in the flask was changed into a jelly-like precipitate. The contents of the flask were removed and pressed through layers of cheese cloth. This removed any unchanged magnesium which would give hydrogen when treated with the acid. The mixture which passed through the cloth was transferred into another three-necked liter flask which was in turn connected to the automatic stirrer and the reflux condenser. As before a thirty percent solution of sulfuric acid was added to remove the jelly-like substance in the flask. The water and ether layers were separated and treated as in protocol two. The carbinol mixture was fractionated and the tarry residue discarded. The following fractions were obtained:

Trial	Temperature	Greatest Yield	Pressure
1.	30-47° C.		7 mm.
2.	47-50° C.		7 mm.
3.	50-55° C.		7 mm.
4.	55-75° C.		7 mm.
5.	75-90° C.		7 mm.
6.	90-104° C.	102° C.	7 mm.
7.	104-112° C.	108° C.	7 mm.
8.	112-115° C.	114° C.	7 mm.
9.	115-120° C.	118° C.	7 mm.
10.	120-125° C.	121° C.	7 mm.

One Carius determination was run on each of the middle fractions. They gave:

Fraction Analyzed	Percentage of Chlorine Found
55-75° C.	52.50
90-104° C.	37.98
104-112° C.	41.90
112-115° C.	38.44
115-120° C.	30.12
120-125° C.	25.47

The chlorine analysis of the fraction boiling between 104° and 112° C. gave the desired results. In order to be sure of this figure, three other determinations were run on this same sample. The chlorine

percentages obtained were 42.63, 42.86, and 42.84. The yield obtained in this protocol was still low so another method was tried.

Protocol 5. In place of the magnesium turnings, magnesium ribbon was used. Six grams of magnesium ribbon were cleaned with emery paper and put into the liter flask. This was treated with forty-six grams of heptyl bromide in seventy-five cubic centimeters of absolute ether. During the addition of the heptyl bromide and ether a more complete reaction was noted. This mixture was refluxed and allowed to stand over night. As before a white precipitate was formed. This mixture was added to thirty-six grams of chloral in seventy-five cubic centimeters of absolute ether. It was refluxed and allowed to stand for twelve hours. The remaining process was like that in protocol four. In the fractionating, the fraction boiling between 110° and 112° C. was removed. This was analyzed by the Carius method and gave a chlorine content of 41.32 and 42.10 percent. This percentage checks very closely with the theoretical one of 42.97. The yield in this protocol was eight grams, which was a large increase over those obtained in protocols one, two, and four.

In determining the properties of trichloromethyl heptyl carbinol aside from the boiling point and chlorine content, the solubility in various solvents, the spe-

cific gravity, and the index of refraction as well as the color, odor, and taste, were determined. It was found that the carbinol was insoluble in water, but soluble in acetone, benzene, carbon disulfide, carbon tetrachloride, chloroform, ethyl alcohol, ether, and methyl alcohol.

The density of the alcohol was determined by means of a specific gravity bulb. This tube, which had a volume of about one-half of one cubic centimeter, was standardized by weighing it first empty and again after it had been filled with distilled water at 20° C. The bulb was then dried and refilled with the alcohol at 20° C., when it was reweighed. The specific gravity, which is equal to the ratio of the weight of the alcohol at 20° C. to the weight of an equal volume of water at the same temperature, was found to be 1.1515.

The index of refraction, which was determined by means of an Abbé refractometer, was found to be 1.4720 at 20.05° C.

The freshly distilled trichloromethyl-heptyl carbinol is a very light yellow, but it turns darker on standing. It has a bitter, oily taste, but a pleasant odor. The alcohol could not be made to crystallize out. A temperature of 0° C. was reached in an attempt to solidify this compound.

Ester Preparation.

The Normal Butyric Ester of Trichloromethyl-heptyl Carbinol

In the preparation of an ester to confirm the fact that trichloromethyl-heptyl carbinol had been prepared, two grams of the carbinol were heated with a fifty percent excess of normal butyryl chloride. This mixture was refluxed for two hours at a temperature of between 130° and 135° C. and then poured into a beaker of water. This was done to destroy the excess of normal butyryl chloride. To the mixture in the beaker, sodium hydroxide was added until the solution was slightly basic. The purpose of this process was to form the sodium salts of the acids, which are insoluble in ether. The ester was extracted with ether from the water solution, and the ether mixture was allowed to dry over anhydrous calcium chloride. The ether was distilled off and the resulting ester was found to boil at 113° C. under a reduced pressure of nine millimeters. An eight percent yield of the ester was obtained. The chlorine content of the normal butyric ester of trichloromethyl-heptyl carbinol was analyzed by the Larius method, and found to confirm with the theoretical percentage of chlorine.

Trial	Percentage Found	Percentage Calculated
1.	34.48	33.50
2.	34.55	

The preparation of the propinoic ester of trichloromethyl-heptyl carbinol was attempted by the same method as was used in the preparation of the butyric ester. Unsatisfactory results were obtained in this case, and limited material prevented another attempt to make this compound.

In determining some of the properties of the butyric ester, the solubility, specific gravity, and index of refraction were found. The ester is insoluble in water but readily soluble in acetone, benzene, carbon disulfide, carbon tetrachloride, chloroform, ethyl alcohol, ether, and methyl alcohol.

The density of the ester was determined by means of a specific gravity bulb. This was found to be 1.0800 at 20° C.

The index of refraction for the ester was found to be 1.4685 at 19.6° C. This figure was obtained by means of an Abbe' refractometer.

The ester is brown in color, has a bitter, oily taste, and has the characteristic butyric odor. The product on standing becomes darker in color.

Conclusion

Trichloromethyl-heptyl carbinol was prepared and studied. Its following properties were found: color, a very light yellow; odor, pleasant; taste, bitter and oily; solubility, insoluble in water, but soluble in acetone, benzene, carbon disulfide, carbon tetrachloride, chloroform, ethyl alcohol, ether, and methyl alcohol; specific gravity, 1.1515 at 20° C.; index of refraction, 1.4720 at 20.35° C.; boiling point, 110-112° C. at 9 millimeters pressure; chlorine content, 42.97 percent. The compound decomposes on standing. The molecular weight which was calculated from the formula was found to be 247.507.

The normal butyric ester of trichloromethyl-heptyl carbinol was prepared and studied. The following properties were found: color, light yellow; odor, characteristic butyric; taste, bitter and oily; solubility, insoluble in water, but soluble in acetone, benzene, carbon disulfide, carbon tetrachloride, chloroform, ethyl alcohol, ether, and methyl alcohol; specific gravity, 1.0200 at 20° C.; boiling point, 118° C. at 9 millimeters pressure; and a chlorine content of 33.50 percent. The calculated molecular weight of the ester was found to be 317.555. The index of refraction was 1.4635 at 19.6° C.

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